

# **9vHPV Vaccine for Mid-Adult Persons (27-45 yo) Results from Clinical Studies**

**Advisory Committee on Immunization Practices**

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# Introduction – 9-valent HPV (9vHPV) Vaccine

- 9vHPV vaccine was licensed for use in 9-26 year olds of both genders
- In 2015, ACIP:
  - Included 9vHPV vaccine in its recommendations for routine HPV vaccination of girls and boys 11-12 years
  - Recommended catch-up vaccination for males up to age 21 years, and for females, MSM and immunocompromised persons (including those with HIV infection) up to age 26 years
- A supplementary application to expand the age indication for 9vHPV vaccine was filed with the FDA in April 2018
  - Current age indication: 9-26 years (males and females)
  - Proposed new age indication: 9-45 years (males and females)\*
  - Expected review time up to 6 months

*\*The 9vHPV vaccine is indicated in girls and women 9-45 years of age in Canada and Australia, and individuals from the age of 9 years in the European Union*

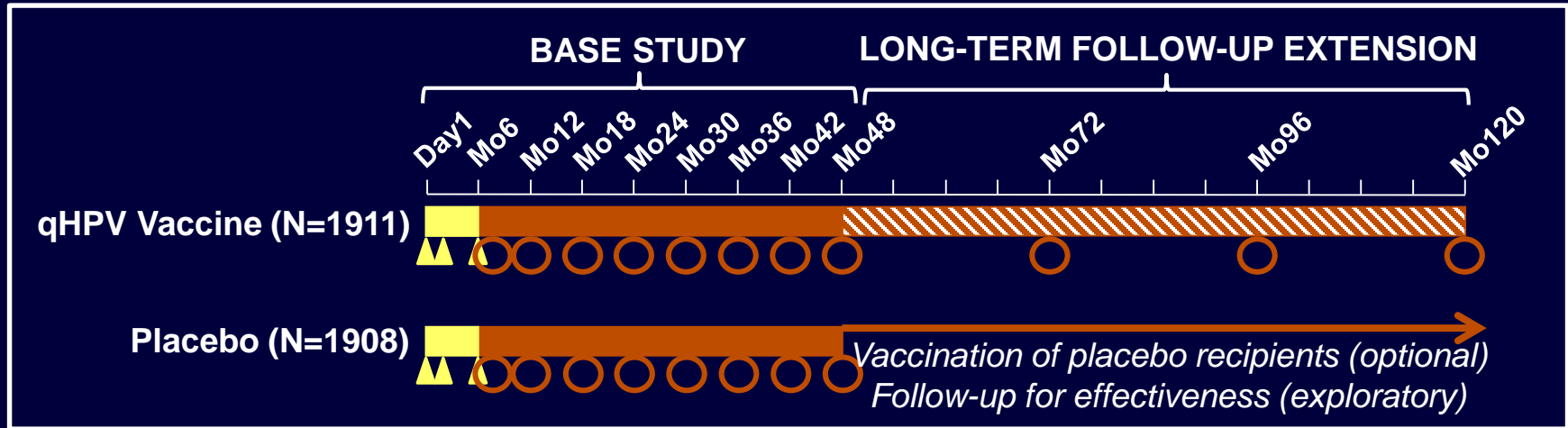
# Clinical Studies Supporting HPV Vaccination of Adults 27-45 Years of Age

- The proposed licensure for use of 9vHPV vaccine among 27- 45-year-olds is based on a Phase 3 study of qHPV vaccine
  - High prophylactic efficacy among 27- to 45-year-old women
  - Durable effectiveness through 10 years of follow-up
- Regulatory agencies have concluded that qHPV vaccine efficacy/immunogenicity results can be bridged to 9vHPV vaccine
  - Both vaccines contain VLPs for HPV6/11/16/18 and are manufactured using similar processes
  - Consistent success in efficacy and immunogenicity bridging studies of qHPV and 9vHPV vaccines across age and gender

# **QHPV VACCINE MID-ADULT STUDIES**

# qHPV Vaccine 10-year Study in 24-45 Year-Old Women

(Protocol V501-019 – NCT00090220)



## STUDY STAGE

- Vaccination period
- Efficacy follow-up period (base study)
- Effectiveness follow-up period (extension)
  - Subset of subjects from Colombia (N=685)

## KEY ACTIVITIES

- Vaccine/placebo administration
- Follow-up visits
  - Serum collection (immunogenicity)
  - Cervical cytology (Pap test)
  - Genital swab (HPV DNA; base study only)

# Base Study: Baseline Characteristics of Randomized Subjects

	qHPV Vaccine (N=1911)	Placebo (N=1908)
	n (%)	n (%)
Mean Age (years $\pm$ sd)	34.3 $\pm$ 6.3	34.3 $\pm$ 6.3
Lifetime no. of sexual partners		
1	713 (37.6)	751 (39.4)
2	385 (20.2)	362 (19.0)
3	229 (12.0)	223 (11.7)
4	142 (7.4)	130 (6.8)
>4	433 (22.7)	437 (22.9)
Median	2	2
Baseline HPV DNA prevalence		
All vaccine types	159 (8.4)	139 (7.4)
HPV 6	34 (1.8)	37 (1.9)
HPV 11	4 (0.2)	5 (0.3)
HPV 16	93 (4.9)	77 (4.0)
HPV 18	39 (2.0)	40 (2.1)
N=number of subjects randomized		
Reference: Castellsague et al. Br J Cancer. 2011;105:28-37		

# Base Study: HPV6/11/16/18-related Persistent Infection (PI), Cervical Disease (CIN), and Condyloma

(24-45 yo women; Per Protocol Efficacy Population)

Endpoint	qHPV Vaccine (N=1910)	Placebo (N=1907)	Efficacy (95% CI)
	Cases/ n	Cases/ n	
6-month PI	<b>9</b> / 1581	<b>85</b> / 1586	<b>89.6%</b> (79.3, 95.4)
CIN (any grade)	<b>1</b> / 1581	<b>17</b> / 1584	<b>94.1%</b> (62.5, 99.9)
≥ CIN 2	<b>1</b> / 1581	<b>6</b> / 1584	<b>83.3%</b> (-37.6, 99.6)
Condyloma	<b>0</b> / 1600	<b>7</b> / 1599	<b>100%</b> (30.8, 100)

*End-of-base study analyses (mean follow-up: 3.8 years)*

N=number of subjects randomized who received ≥1 injection

n=number of subjects who had ≥1 follow-up visit after Month 7

*Reference: Castellsague et al. Br J Cancer. 2011;105:28-37*

## Base Study: Vaccine-related AEs (24-45 yo Women)

Type of AE	qHPV Vaccine (N=1889)	Placebo (N=1886)
	n (%)	n (%)
Number (%) of subjects		
With injection-site AE*	1443 (76.4)	1210 (64.2)
Injection-site pain	1423 (75.3)	1170 (62.0)
Severe	60 (3.2)	33 (1.7)
Injection-site swelling	353 (18.7)	214 (11.3)
Severe (>2 inches)	28 (1.5)	14 (0.7)
Injection-site erythema	273 (14.5)	200 (10.6)
Severe (>2 inches)	11 (0.6)	6 (0.3)
With vaccine-related systemic AE**	745 (39.4)	695 (36.9)
Headache	401 (21.2)	375 (19.9)
Pyrexia	178 (9.4)	170 (9.0)
With serious AE***	0 (0.0)	0 (0.0)
Who discontinued due to an AE**	5 (0.3)	1 (0.1)

Based on a visit cut-off date of 13-Jul-2007

N=number of subjects who received ≥1 injection and had safety follow-up

\*Days 1-5 after any vaccination; \*\*Days 1-15 after any vaccination; \*\*\*Entire study duration



# Long Term Follow-up Extension: Data Analysis [1 of 2]

- When the base study was finished, placebo-recipients were offered vaccine
- A cohort of 685 Colombian subjects who received qHPV vaccine in the base study consented to participate in a long-term extension for a total of 10 years of follow-up
  - 651 Colombian subjects who received placebo in the base study and qHPV vaccine after the base study were also followed in the extension for exploratory analyses
- Vaccine effectiveness was evaluated in these subjects
  - Primary effectiveness endpoint: HPV6/11/16/18-related CIN or condyloma
  - Primary analysis population: per-protocol effectiveness population
    - Received 3 doses of qHPV vaccine within 1 year in the base study
    - Seronegative at Day 1 and PCR negative Day 1 through Month 7 for the HPV type being analyzed
  - The cumulative probabilities of acquiring the primary endpoint in the primary analysis population during the relevant study periods were calculated

## Long Term Follow-up Extension: Data Analysis [2 of 2]

- The overall study was conducted in women 24-45 years at enrollment
- 9vHPV vaccine is recommended in girls/women 9-26 years; therefore, the analyses are presented only in women 27-45 years at enrollment
  - 600 subjects 27-45 year old at enrollment who received qHPV vaccine in the base study and continued in the LTFU study
  - Follow-up for effectiveness of these subjects (in the base study and LTFU study combined) up to 10.1 (median: 8.9) years post-dose 3

# Efficacy of qHPV Vaccine in Women 27-45 Years at Enrollment in the Base Study

## *Per-protocol Efficacy Population*

Endpoint	qHPV Vaccine (N=1624)	Placebo (N=1629)	Efficacy (95% CI)
	Cases/ n	Cases/ n	
HPV6/11/16/18-related CIN, and condyloma	<b>1 / 1376</b>	<b>20 / 1384</b>	<b>95.0%</b> (68.7, 99.9)
<p>End-of-base study analyses (median follow-up: 3.9 years)</p> <p>N=number of subjects randomized who received <math>\geq 1</math> injection</p> <p>n=number of subjects who had <math>\geq 1</math> follow-up visit after Month 7</p>			

# Cumulative Incidence of HPV6/11/16/18-related CIN or Condyloma in 4-Year Intervals of LTFU Study vs Base Study (27-45 yo at Day 1; Per Protocol Efficacy Population)

Time from Dose 1	qHPV Vaccine in base study (N=1624)		Placebo in base study (N=1629)	
	Cases/ n	Cumulative Incidence Probability Estimate* <sup>†</sup> (95% CI)	Cases/ n	Cumulative Incidence Probability Estimate* <sup>†</sup> (95% CI)
Day 1 to Year 4				
All subjects	1 / 1377	0.7 (0.1, 5.2)	16 / 1384	12.1 (7.4, 19.7)
Non-Colombia	1 / 778	1.3 (0.2, 9.2)	5 / 759	6.8 (2.8, 16.2)
Colombia	0 / 599	0.0	11 / 625	17.9 (10.0, 32.2)
Year 4 to Year 8	0 / 804	0.0	—	—
Year 6 to Year 10	0 / 527	0.0	—	—

\*Cumulative incidence probability expresses the probability (in the population) of acquiring the disease endpoint during the time interval indicated in the corresponding row.

<sup>†</sup> In  $10^{-3}$  units ( e.g., 0.7 in  $10^{-3}$  units= 0.0007)

# Cumulative Incidence of HPV31/33/35/39/45/51/52/56/58/59-related CIN or Condyloma in 4-Year Intervals of LTFU Study vs Base Study

(27-45 yo at Day 1; Naïve to the Relevant HPV Type Population)

Time from Dose 1	qHPV Vaccine in base study (N=1624)		Placebo in base study (N=1629)	
	Cases/ n	Cumulative Incidence Probability Estimate*† (95% CI)	Cases/ n	Cumulative Incidence Probability Estimate*† (95% CI)
Day 1 to Year 4				
All subjects	26 / 1586	17.8 (12.1, 26.0)	27 / 1578	18.5 (12.7, 26.9)
Non-Colombia	11 / 907	14.2 (7.8, 25.7)	10 / 887	12.1 (6.5, 22.4)
Colombia	15 / 679	22.8 (13.8, 37.6)	17 / 691	25.4 (15.8, 40.5)
Year 4 to Year 8	3 / 888	4.8 (1.3, 13.3)	—	—
Year 6 to Year 10	4 / 576	10.8 (3.4, 27.3)	—	—

\*Cumulative incidence probability expresses the probability (in the population) of acquiring the disease endpoint during the time interval indicated in the corresponding row.

† In  $10^{-3}$  units (e.g., 17.8 in  $10^{-3}$  units= 0.0178)

# Summary of 10-year Study of qHPV Vaccine in Women 27-45 Years

- Durable effectiveness through 10 years
  - No cases of HPV6/11/16/18-related cervical disease and condyloma during the study extension
  - Continued exposure to non-vaccine HPV types (absence of HPV disease is not due to lack of HPV exposure)
  - Follow-up through 10.1 years (median 8.9 years)
- Sustained immunogenicity through 10 years post vaccination onset
- qHPV vaccine generally well-tolerated
  - No vaccine-related serious AE during the entire study

# Post-hoc Immunogenicity Bridging Analyses

## Cross-study Comparison of qHPV Vaccine Trials

### STUDIES INCLUDED IN THE ANALYSES

Study	Population
Protocol V501-013 (aka FUTURE I)	16-26 yo women
Protocol V501-015 (aka FUTURE II)	16-26 yo women
Protocol V501-019 (aka FUTURE III)	24-45 yo women
Protocol V501-020	16-26 yo men
Protocol V501-108 (aka the MAM study)	27-45 yo men

#### References:

- V501-013 (NCT00092521): Garland et al. N Engl J Med. 2007;356:1928–1943
- V501-015 (NCT00092534): FUTURE II Study Group. N Engl J Med. 2007;356:1915–1927
- V501-019 (NCT00090220): Muñoz et al. Lancet. 2009;373:1949–1957
- V501-020 (NCT00090285): Giuliano et al. N Engl J Med. 2011;364:401–411  
Palefsky et al. N Engl J Med. 2011;365:1576–1585
- V501-108 (NCT01432574): Giuliano et al. (2015) Vaccine 33:5640-5646.

# Post-hoc Immunogenicity Bridging Analyses

## Cross-study Comparison of qHPV Vaccine Trials

- **Objective**
  - Comparison of HPV6, 11, 16, and 18 GMTs at 1 month post-dose 3 between 27-45 year-olds and 16-26 year-olds
  - Non-inferiority criterion: lower bound of the 95% CI of the GMT ratio (27-45 yo / 16-26 yo)  $>0.67$
- **Populations analyzed**
  - Women
    - ✓ 27-45 yo women from FUTURE III
    - ✓ 16-26 yo women pooled from FUTURE I, FUTURE II, and FUTURE III
  - Men
    - ✓ 27-45 yo men from Protocol V501-108 (aka the MAM Study)
    - ✓ 16-26 yo men from Protocol V501-020



## Non-inferior GMTs at Month 7 in 27-45 yo Women vs. 16-26 yo Women who Received qHPV Vaccine

Assay (cLIA)	27-45 yo women (Group A)		16-26 yo women (Group B)		Group A / Group B
	n	GMT	n	GMT	GMT ratio (95% CI)
Anti-HPV 6	1083	412.4	2800	536.2	0.77 (0.72, 0.82)
Anti-HPV 11	1083	538.2	2824	754.3	0.71 (0.67, 0.76)
Anti-HPV 16	1092	2212.0	2749	2297.6	0.96 (0.89, 1.05)
Anti-HPV 18	1223	348.4	3006	458.1	0.76 (0.71, 0.82)

Conclusions: non-inferiority was demonstrated for the 4 HPV types; based on these results, efficacy results previously established in 16-26 yo women are extended to 27-45 yo women

## Non-inferior GMTs at Month 7 in 27-45 yo Men vs. 16-26 yo Men who Received qHPV Vaccine

Assay (cLIA)	27-45 yo men (Group A)		16-26 yo men (Group B)		Group A / Group B
	n	GMT	n	GMT	<b>GMT ratio (95% CI)</b>
Anti-HPV 6	147	420.0	1092	447.6	<b>0.94 (0.76, 1.15)</b>
Anti-HPV 11	147	514.5	1092	624.0	<b>0.82 (0.70, 0.98)</b>
Anti-HPV 16	147	2481.3	1135	2404.3	<b>1.03 (0.85, 1.26)</b>
Anti-HPV 18	147	302.6	1174	402.3	<b>0.75 (0.61, 0.93)</b>

Conclusions: non-inferiority was demonstrated for HPV types 6, 11, and 16; based on these results, efficacy results previously established in 16-26 yo men are extended to 27-45 yo men

**SIMILAR EFFICACY, IMMUNOGENICITY, AND  
SAFETY OF 9vHPV AND qHPV VACCINES IN 9  
TO 26 YEAR OLDS**

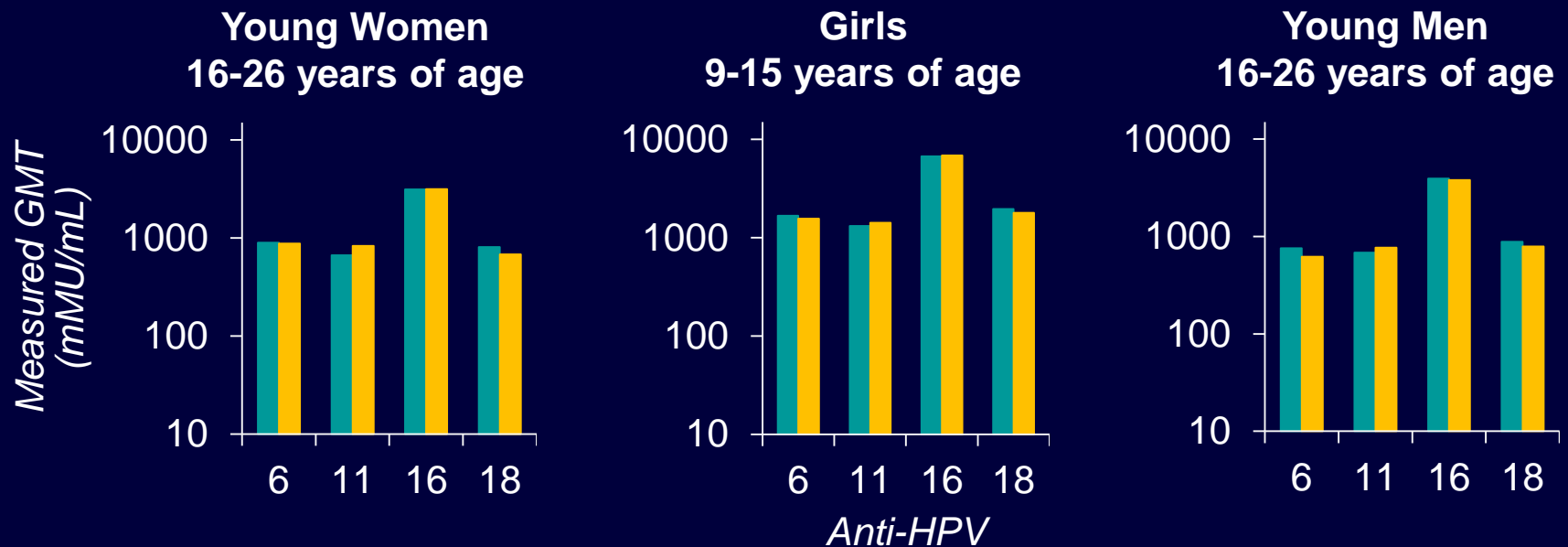
# Bridging Efficacy, Immunogenicity and Safety Across Vaccines and Across Genders

- Efficacy of qHPV vaccine against HPV6/11/16/18-related disease
  - ✓ Demonstrated in clinical studies in women 16-26 years, women 27-45 years and men 16-26 years
- Efficacy of 9vHPV vaccine against HPV6/11/16/18-related disease
  - ✓ Inferred based on non-inferior HPV6/11/16/18 antibody response in 9vHPV vaccine group vs. qHPV vaccine group (regardless of age and gender)
  - ✓ Further supported by observation of similar, low incidence of HPV6/11/16/18-related disease in a clinical study in 16-26 yo women
- Generally comparable adverse event profile with 9vHPV and qHPV vaccine
  - ✓ More injection-site AEs, mostly mild or moderate in intensity
  - ✓ Adverse events less frequent in men than in women

*Ref: Luxembourg A, Moeller E. Expert Rev Vaccines 2017; 16: 1119–39.*

# Non-inferiority of Month 7 cLIA GMT in 9vHPV Vaccine Group vs. qHPV Vaccine Group

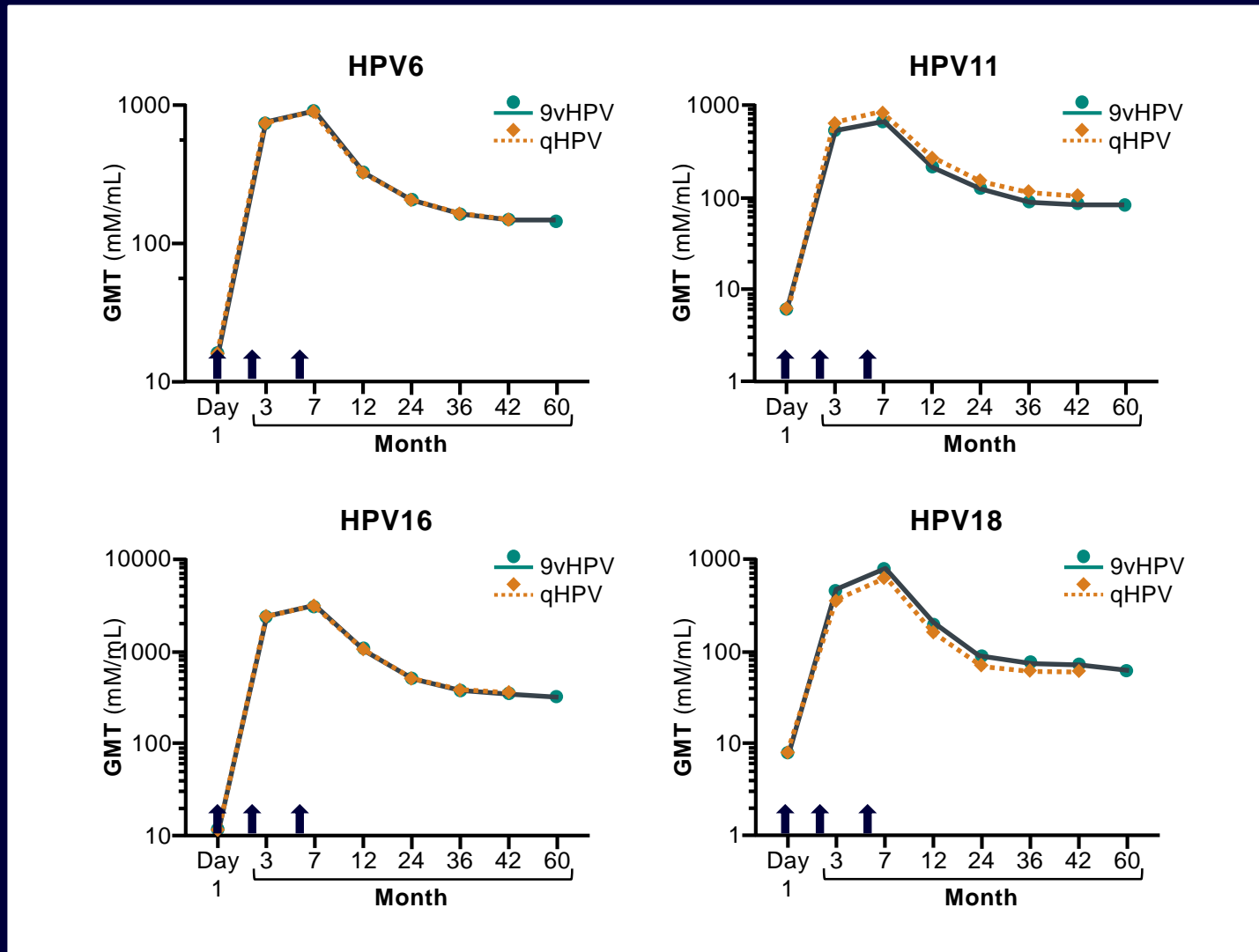
- Three clinical studies in 3 demographic groups showed non-inferior immunogenicity of 9vHPV vaccine versus qHPV vaccine
  - Comparison at month 7 (1 month post-dose 3) for all 3 studies (see below)
  - Assessment over time in young women 16-26 years of age (next slide)



■ 9vHPV ■ qHPV

Joura et al. N Engl J Med. 2015;372:711–723  
Vesikari et al. Pediatr Infect Dis J. 2015;34:992–998  
Van Damme et al. Vaccine. 2016;34:4205–4212.

# Similar HPV6/11/16/18 Antibody Response Profiles for 9vHPV Vaccine and qHPV Vaccine Over Time (Women 16-26 years of age)



↑: Vaccination visits at Day 1, Month 2, and Month 6.

# Similar Protection Against HPV6/11/16/18 Disease Endpoints with 9vHPV Vaccine and qHPV Vaccine

## 16-26 yo women – Per-Protocol Efficacy Population

Endpoint	9vHPV vaccine clinical program*		qHPV vaccine clinical program**	
	9vHPV	qHPV	qHPV	Placebo
	Cases/total	Cases/total	Cases/total	Cases/total
Low-grade cervical disease	<b>0</b> / 5824	<b>2</b> / 5832	<b>7</b> / 7629	<b>168</b> / 7632
High-grade cervical disease	<b>1</b> / 5824	<b>1</b> / 5832	<b>2</b> / 7864	<b>110</b> / 7865
High-grade vulvar disease	<b>0</b> / 5876	<b>0</b> / 5893	<b>0</b> / 7900	<b>13</b> / 7902
High-grade vaginal disease	<b>0</b> / 5876	<b>2</b> / 5893	<b>0</b> / 7900	<b>10</b> / 7902
Genital warts	<b>5</b> / 5876	<b>2</b> / 5893	<b>2</b> / 7665	<b>190</b> / 7669

\*Based on up to 67 months of follow-up post-dose 3 (median 43 months)

\*\*Based on average of 42 months of follow-up post-dose 3

References: FUTURE I/II Study Group BMC 2010; 341:c3493; Kjaer et al. Cancer Prev Res (Phila); 2009;2:868–878; Huh et al. Lancet 2017; 390:2143-2159.

# CONCLUSIONS



# Conclusions

- Efficacy/effectiveness
  - qHPV vaccine prevents HPV6/11/16/18-related CIN and condyloma through at least 10 years post vaccination in women 27-45 years of age
- Immunogenicity
  - qHPV vaccine elicits HPV6/11/16/18 antibody responses in women and men 27-45 years of age that are non-inferior to antibody responses in women and men 16-26 years of age
    - These results support efficacy in women and men 27-45 years of age
- Safety
  - qHPV vaccine is generally well tolerated in women/men 27-45 years of age
- Relevance to 9vHPV vaccine
  - Clinical experience with qHPV vaccine is relevant to 9vHPV vaccine
    - Consistent immunogenicity, efficacy, and safety profile of the 2 vaccines
    - Both vaccines contain VLPs for HPV6/11/16/18 and are manufactured using similar processes
  - Therefore, these results are deemed applicable to 9vHPV vaccine

# Ongoing 9vHPV Vaccine Study

- Protocol V503-004 (CT.gov identifier: NCT03158220)
  - Post-marketing study requested by the EMA
- Study population
  - 27-45 yo women (N=600)
  - 16-26 yo women (N=600) (control group)
- Vaccine administration
  - 9vHPV vaccine; standard 3-dose regimen (day 1, months 2 and 6)
- Primary objective
  - Demonstrate non-inferior GMT at Month 7 in 27-45 yo women versus 16-26 yo women for the 7 high-risk types in the vaccine
- Timeline
  - Analyses expected in 2Q2019